Remarks

Claims 1-43, 72-75, 83-91, and 133-143 are pending. Claims 44-71, 76-82 and 92-132 have been withdrawn from consideration.

Summary of Interview

Applicants would like to thank Examiner Hama and Supervisor Paras for their comments during the telephone interview of March 7, 2007 to discuss the Office Action mailed October 4, 2006. Applicants believe that there has been a miscommunication of the enablement and written description requirements as they apply to the present claims that has resulted in the instant enablement and written description rejections. An attempt to clarify the record is provided herein. In addition, the Office is apparently resistant to grant claims based on the level of sequence identity to which the Applicants believe they are entitled. Applicants' arguments for the allowance for claims directed to nucleic acids encoding HEX proteins which have at least 70% sequence identity to provided sequences are clarified herein. However, it is noted that in the response filed July 27, 2006 Applicants amended the claims to separately recite 95%, 85%, and 70% sequence identities in order to facilitate prosecution and allowance.

I. Rejection under 35 U.S.C. § 112, first paragraph - Enablement

A. Claims 1-43, 72-75, 83-91, and 133-143 remain rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the enablement requirement.

1. Structure and Function

The Applicants believe there has been a miscommunication in the record and a misunderstanding as to the claims reciting sequence identity. In the telephone interview of April 14, 2006, Examiner Hama discussed her concerns regarding the scope of the sequence identity claims and indicated that the Applicants should include a functional limitation so that the skilled artisan could know whether a mutant form of HEX-alpha or HEX-beta can be used in the claimed compositions and methods. In order to facilitate prosecution, the Applicants amended the claims to

separately recite 95%, 85%, and 70% sequence identities and added a functional limitation to claims 1 and 72, i.e., the ability to catabolize GM_2 ganglioside.

However, the Examiner has apparently interpreted this amendment as intending to cover any mutant, stating "screening without guidance as to what structure of HEXA and HEXB would need to be conserved to arrive at a functional protein is not enabled." Thus, the Applicants would like to clarify their position on why the claims are in fact enabled.

First, the Applicants are claiming a genus of molecules based on structure and function. The structure of HEX-alpha and HEX-beta were known and described in the specification. In addition, claims stand rejected (see claim 138) that restrict the structure of HEX-alpha and HEX-beta to a sequence identity of as high as 95% to the known structure. The Examiner has characterized this as "screening for mutants that fit the functional criteria" and stated that this does not enable an artisan to arrive at the claimed invention. However, the claim is not to a product-by-process resulting from a screening method. Rather, a genus of molecules is provided based on the known structure of HEX-alpha and HEX-beta, and a function, i.e., the ability to catabolize GM_2 ganglioside, is provided to guide the skilled artisan to avoid variants that would not have the utility disclosed in the specification. This does not constitute a screening process, because the genus of compounds is defined by structure. For example, the sequence for HEX-β is set forth in SEQ ID NO:3 and the sequence for HEX-α is set forth in SEQ ID NO:1. Thus, reference sequences are provided for HEX-β and HEX-α, which defines the structure of these proteins and the nucleic acids that encode them. A genus of compositions is therefore provided based on variance of these structures. For example, claim 12 recites that "the HEX-β has at least 70% identity to the sequence set forth in SEQ ID NO:3 and the HEX-α has at least 70% identity to the sequence set forth in SEQ ID NO:1." In addition, claim 138 limits the sequence identity to 95%. Thus, the genus of compositions are varied only by sequence identity to this known structure.

Second, Applicants submit that the present rejection depends only on the question of whether, in view of the specification and the knowledge of those of skill in the art at the time the invention was made (as evidenced by the complete record in this application), the compositions of

claims 1-43, 72-75, 83-91, and 133-143 could be made and used by those of skill in the art without the need for undue experimentation.

a) The Legal Standard

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the specification, coupled with information known in the art, without undue experimentation. See United States v. Telectronics, Inc., 857 F.2d 778, 8 USPQ2d 1217 (Fed. Cir. 1988); In re Stephens, 529 F.2d 1343, 199 USPQ 659 (CCPA 1976). Determining enablement is a question of law based on underlying factual findings. In re Vaeck, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991); Atlas Powder Co. v. E.I. duPont de Nemours & Co., 750 F.2d 1569, 224 USPQ 409 (Fed. Cir. 1984).

One determines undue experimentation not by analyzing a single factor, but rather by analyzing and weighing many factors. The legal standard set out in *In re Forman* 230 U.S.P.Q. 564, 547 (Bd. Pat. App. & Int. 1986) and elucidated in *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400 (Fed. Cir. 1988) sets forth the following factors for consideration: (1) The quantity of experimentation necessary (time and expense); (2) The amount of direction or guidance presented; (3) The presence or absence of working examples of the invention; (4) The nature of the invention; (5) The state of the prior art; (6) The relative skill of those in the art; (7) The predictability or unpredictability of the art; and (8) The breadth of the claims. It is not necessary that every enablement analysis consider all of the factors. *Amgen, inc. v. Chugai Pharmaceutical Co., LTD.*, 927 F.2d 1200, 1213 (Fed. Cir. 1991).

The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *M.I.T. v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 190 U.S.P.Q. 214 (CCPA 1976).

The facts underlying the decision of *In re Wands* illustrate well the concepts put forth in *MIT. A.B. Fortia* and *In re Angstadt.* The method claims at issue in *Wands* involved the use of an antibody wherein the "antibody is a monoclonal high affinity IgM antibody having a binding

affinity constant for . . . [the antigen] of at least 10^9M^{-1}." *In re Wands*, 858 F.2d at 734. This claim covers *any* monoclonal antibody, not just a specific monoclonal antibody, and the PTO argued that the Applicant failed to enable *all* monoclonal antibodies. *Id.* Briefly, the skilled artisan generates monoclonal antibodies by injecting an antigen into a host animal causing an immune reaction, isolating spleen cells, some of which produce the antibodies that bind the antigen, fusing the spleen cells with a cancerous myeloma cell producing a hybridoma, and then screening individual hybridomas to isolate those that produce antibodies that bind the antigen. *Id.* at 733-734. The PTO supported its non-enablement position by pointing out that 1) not all hybridomas produce antibodies that bind antigen, 2) not all hybridomas that bind antigen will bind with an affinity of 10^9M^{-1}, and 3) the Applicants own data indicated that a small percentage of hybridomas actually produced monoclonal antibodies which fell within the scope of the claims. *Id.* at 738-739. The court rejected these arguments by stating,

> cell fusion [hybridoma technology] is a technique that is well known to those of skill in the monoclonal antibody art, . . .[t]here was a high level of skill in the art at the time when the application was filed, and all the methods needed to practice the invention were well known . . . [and] it seems unlikely that undue experimentation would be defined in terms of the number of hybridomas that were never screened, . . .[and since] Wands carried out his entire procedure three times, and was successful each time in making at least one antibody that satisfied all of the claim limitations . . . Wands evidence thus effectively rebuts the examiner's challenge to the enablement of their disclosure.

Id. at 740. Furthermore, the Wands court made clear that the amount of and type of experimentation considered undue fluctuates for each type of art. *Id.* The quantity of experimentation lacks relevance outside an assessment of what is "routine experimentation" in the art. *Id.* Thus, the huge amount of "experimentation" that the skilled artisan would have to perform to practice Wands' invention: immunizing an animal, fusing lymphocytes from the immunized animals with myeloma cells to make hybridomas, cloning the hybridomas, and screening the hybridomas for the desired characteristics, *knowing that many hybridomas would not produce functional antibodies and* ***not*** *knowing which hybridomas would produced claimed antibody*, was not undue experimentation because it was routine experimentation in the art of monoclonal antibody production. *Id.* As discussed below, the present claims and corresponding enablement rejection closely parallel the situation presented in *Wands* since the art of producing the presently

claimed nucleic acid compositions encoding the genus of Hex proteins that have the disclosed catabolic activity is routine experimentation in the art of recombinant nucleic acid and peptide design, even though it may seem complex.

The fact that experimentation may be complex does not necessarily make it undue if the art typically engages in such experimentation. See M.I.T. v. A.B. Fortia, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. See In re Angstadt, 537 F.2d 498, 190 USPQ 214 (CCPA 1976).

> "The test [for undue experimentation] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed."
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> PPG Indus., Inc. v. Guardian Indus. Corp., 75 F.3d 1558, 1564, 37 U.S.P.Q.2d 1618, 1623 (Fed. Cir. 1996)(internal quotes and citation omitted).

b) Predictability of Function based on Sequence Identity

As noted below, the predictability for the function of a protein having at least 70% sequence identity to a known protein is greater than 90%. And, this assumes that no specific information regarding conserved regions of the protein are known, i.e., random mutations. However, specific mutations in HEX-alpha and HEX-beta that cause neurological disorders were known in the art. For example, mutations of the HexA gene are known that result in Tay-Sachs disease (see Gravel et al. 1991, Ref.# A50 of IDS filed February 18, 2004), and mutations of the HexB gene are known that result in Sandhoff's disease (See Neufeld EF. J Biol Chem. 1989 Jul 5;264(19):10927-30, attached hereto as Exhibit A). Thus, the skilled artisan would know to at least avoid these specific mutations, making the predictability even higher.

Applicants appreciate the difficulty in determining the appropriate breadth of sequence identity that should be considered enabled and patentable. Applicants have made a case to support the predictability for sequence variants of at least 70% identity. However, the Examiner has apparently mis-interpreted the Applicant's summary of the findings of Tian and Skolnick (J Mol

Biol. 2003 Oct 31;333(4):863-82) used to support this position. Specifically, the Applicants noted that most (~90%) mutants will maintain enzyme function with sequence identities as low as 60%. This is based on the finding by Tian and Skolnick (page 876, second paragraph) that all four numbers of an EC number, stating "above 60% sequence identity is needed to have above 90% accuracy." The Applicants further noted that in fact enzyme function does not generally *start* to diverge until the sequence identity is below 70% (See Tian and Skolnick, abstract, page 863). However, in response, the Examiner stated that "while "most" protein mutants may maintain enzyme function, the assertion does not indicate to an artisan how to discriminate the 10% of mutants which do no have activity."

First, while the Applicant believes that the 90% predictability combined with the level of skill of the artisan for assaying GM_2 ganglioside catabolysis, would not constitute undue experimentation, this predictability is actually based on 60% sequence identity. In contrast, the lowest percent identity claimed by the Applicant is 70%, and there is no evidence, either in Tian and Skolnick or in the art, that any mutations within this range, other than the one's already known in the art to cause disease, would in fact result in a non-functional mutant. Again, Tian and Skolnick report that enzyme function *starts* to diverge when the sequence identity is below 70%. Thus, the Applicant would expect with a very high level of certainty that any given sequence would function, and the skilled artisan would likely never pick a sequence that would not function. Further, while the skilled artisan has a high expectation that any given sequence having 70% identity would function, if needed, it is routine experimentation for one skilled in the art to test such variants to determine if they fit into the claimed homology and to assay said variant for functionality (e.g., GM_2 catabolysis). Thus, as in Wands, where the screening for IgM antibodies with a threshold binding affinity constant was determined not to require undue experimentation since the level of skill was high and the methods were well known, the assaying of candidate peptides for GM_2 catabolysis also requires no more than routine experimentation since there is a high level of predictability that a given peptide within the defined genus will function.

Thus, Applicants believe they have enabled the full scope of compositions based on 70% sequence identity. However, to facilitate prosecution, claim 73 alternatively recites 80% sequence identity, claim 135 alternatively recite 85% sequence identity, and claims 138 and 142 alternatively

recite 95% sequence identity. Applicants request that these alternative scopes be given due consideration.

B. Claim 1 was newly rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the enablement requirement. Specifically, the Examiner notes that claim 1 does not recite a promoter driving the expression of HEX-alpha or HEX-beta, and posits that a skilled artisan would not have predicted expression of the HEX proteins in the absence of expression elements such as a promoter.

The Applicants do not agree that a promoter driving expression of the nucleic acids encoding HEX proteins is necessary to enable the composition. Again, the standard for determining a lack of enablement is whether undue experimentation is required to make or use the composition. In that regards, gene constructs are routinely provided as cassettes for transfer to selected expression vectors. And, the selection of an appropriate expression vector and the transfer of a cassette into the vectors such that it is functionally linked to a promoter are routine, predictable, and require only ordinary skill in the art.

Accordingly, the Applicant respectfully requests the withdrawal of the above rejections, and allowance of claims 1-43, 72-75, 83-91, 133-143.

II. Rejection under 35 U.S.C. § 112, first paragraph - Written Description

Claims 1-43, 72-75, 83-91, and 133-143 remain rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the written description requirement. Specifically, the Examiner states that "nothing in the specification or the art indicate what region(s) of HEX-alpha or HEX-beta is the domain(s) that provide the activity of catabolizing GM_2, such that an artisan could reasonably predict that targeting certain residues would affect enzymatic activity" and that "screening for these mutants based on enzymatic activity is not adequate written description."

The Examiner supports this position by citing MPEP 2163, which states that "[a]n adequate written description also requires a precise definition, such as by structure, formula, chemical name, or physical properties, and not merely a wish or plan for obtaining the chemical invention claimed." (emphasis provided). The MPEP supports this position by citing Univ. of Rochester v. G.D. Searle

& Co., 358F.3d 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004), noting that the patent at issue provided only a description of assays for screening compounds to identify those that could be used in the claimed method. While this is the correct standard for written description, it is also not contrary to the present claims.

First, the instant claims do not attempt to define the composition with only a wish or plan. The above argument would only be valid if the claim were to a composition comprising a nucleic acid encoding any protein that catabolizes GM_2 ganglioside, i.e., with no structural limitation. Such a claim would be attempting to describe the composition entirely by function and/or by a means of identifying compositions having that function. In contrast, the present claims are limited to nucleic acids encoding HEX-alpha and HEX-beta, which have a defined structure. In addition, claims stand rejected that define the structure by sequence identity. The USPTO has already established that variants can be claimed based on sequence identity (see Example 14 of the U.S.P.T.O. "Synopsis of Application of Written Description Guidelines"), wherein it is stated:

> "[t]he single species disclosed is representative of the genus because all members have at least 95% structural identity with the reference compound and because of the presence of an assay which applicant provided for identifying all of the at least 95% identical variants...which are capable of the specified catalytic activity." (page 54, fourth paragraph)

The issue then becomes, if the principle of defining a genus of genetically related compositions by their sequence identity is a viable way of describing a genus because the members of the genus all have a common structural identity, then the only thing left is the extent of the sequence identity that should be allowed. As argued above, the Applicants believe they are entitled to the full scope of 70% sequence identity. If there is adequate written description based on 95%, then there is no clear reason why this should not also extend to 70%. As noted above in the Synopsis of Application of the Written Description Guidelines, a single species can be representative of a genus where all members have at least 95% sequence identity with the reference compound. This is based on the presumption that the skilled artisan would conclude that the Applicant was in possession of the necessary common attributes possessed by the members of the genus. (See *Id*). However, if the function of members of a genus having at least 70% sequence identity with the reference compound is no less predictable, then the skilled artisan would be no less

inclined to assume that the Applicant was in possession of the necessary attributes possessed by the larger genus. Thus, satisfaction of the written description requirement, i.e., possession of the genus of compounds, is a sliding scale that is determined by the predictability that the reference compound is in fact representative of the genus. Applicants believe they have provided sufficient evidence that, absent evidence to the contrary, a specific amino acid sequence for a given enzyme should be considered representative of a genus of members having at least 70% sequence identity with the reference compound.

However, to facilitate prosecution, claim 73 alternatively recites 80% sequence identity, claim 135 alternatively recite 85% sequence identity, and claims 138 and 142 alternatively recite 95% sequence identity. The Applicants request that these alternative scopes be given due consideration.

In addition, at the behest of the Examiner, Applicants amended claims 1 and 72 in the response filed July 27, 2006 to recite a functional limitation, i.e., the ability to catabolize GM_2 ganglioside. This is consistent with the Guidelines shown above, wherein an assay is provided for identifying variants with a disclosed catalytic activity. However, the Applicants do not believe it is necessary to recite this catalytic activity in the claim to satisfy the written description requirement and are willing to discuss amending the claims to remove this limitation if it will advance prosecution.

Accordingly, the Applicant respectfully requests the withdrawal of the rejection, and allowance of claims 1-43, 72-75, 83-91, 133-143.

A Credit Card Payment authorizing payment in the amount of $510.00, representing the fee under 37 C.F.R. § 1.17(a)(3) for a Three Month Extension of Time, a Request for Extension of Time, and Exhibit A as cited on Page 6 of this Amendment, are hereby enclosed. This amount is believed to be correct; however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No.14-0629.

Respectfully submitted,

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P. Brian Giles, Ph.D.

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